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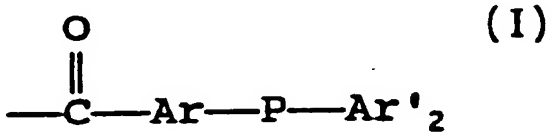
(54) Title: ASYMMETRIC LIGANDS USEFUL FOR TRANSITION METAL CATALYZED BOND FORMING REACTIONS



(I)

(57) Abstract

Ligands useful for transition metal catalyzed bond forming reactions are provided with a metal binding portion having at least one metal binding moiety (I), wherein Ar and Ar' each is an aryl or a heteroaryl. These ligands may be prepared by providing an aromatic carboxylic acid having a diarylphosphino or diheteroarylphosphino substituent on the aromatic ring, and forming an ester or an amide derivative of the carboxylic acid by coupling with a chiral diol or a chiral diamine. The ligands facilitate flexible strategies for enantiocontrolled construction of five membered carbocyclic rings with varying substitution patterns and high enantioselectivity.

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ASYMMETRIC LIGANDS USEFUL FOR TRANSITION METAL CATALYZED BOND FORMING REACTIONS

Field of the Invention.

The present invention generally relates to use of ligands for transition metal catalyzed reactions, and more particularly relates to a new class of asymmetric ligands preferably derived from 2-diphenylphosphino-benzoic acid as an ester or amide from chiral alcohols and chiral amines.

Background of the Invention.

The burgeoning use of transition metals in organic synthesis stems from their ability to orchestrate bond-forming and bond-breaking processes which fall outside the realm of traditional organic chemistry. Such transition metal-mediated reactions offer the unique opportunity to allow asymmetric molecules to participate in a bond breaking and/or making process in an organized manner by coordinating to the active metal center. The importance of absolute stereochemistry and the difficulty of obtaining homochiral compounds by traditional methods has provided the motivation for developing new methods for the creation of chirality.

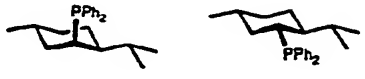
Enantioselective catalysis in general hinges upon the ability to convert enantiotopic transition states into diastereotopic transition states by the introduction of complementary stereogenic centers into the active catalyst. The energy difference between the

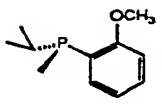
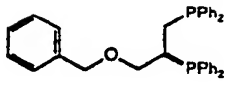
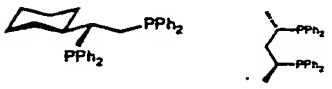
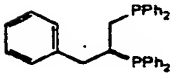
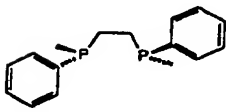
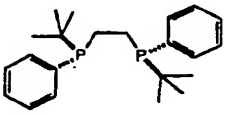
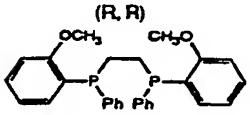
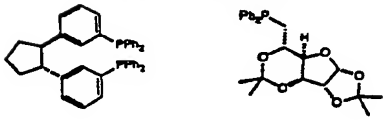
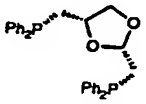
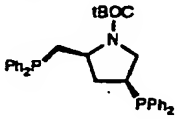
diastereotopic transition states ($\Delta\Delta G^{\ddagger}$) thus determines the enantioselectivity in the reaction. Small energy differences between the two transition states translate into relatively large differences in enantiomeric excess. The vast majority of unoptimized asymmetric metal-catalyzed reactions reported in the literature have enantiomeric excesses below 80%.

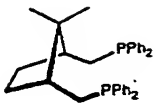
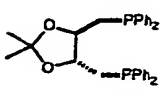
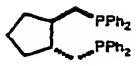
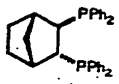
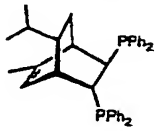
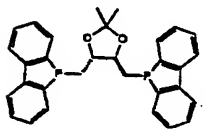
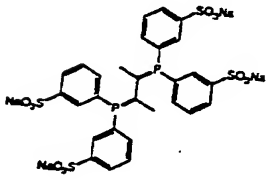
Among the many bond forming reactions where chiral ligands can be used in transition metal catalysis is in the synthesis of glycosidase inhibitors. These molecules have a number of functionalities and rich stereochemistry, which make them extremely challenging targets for total synthesis.

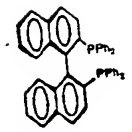
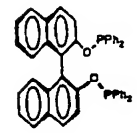
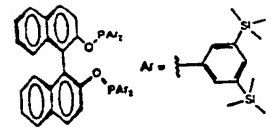
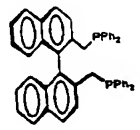
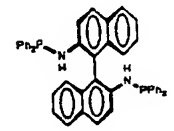
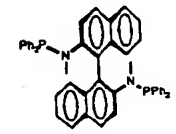
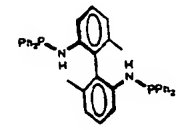
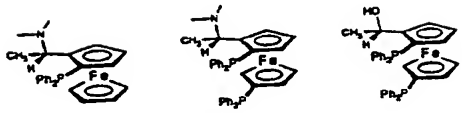
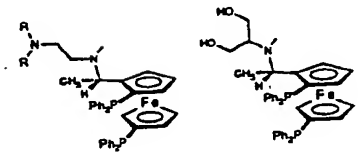
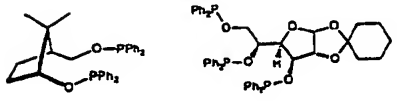
In enantioselective transition metal catalyzed reactions, the use of asymmetric ligands is essential (either as a temporary template to create a chiral complex or as a permanent part of the metal complex) since stereogenic metal centers cannot be readily derived from the chiral pool. Phosphines play an important part in transition metal chemistry because of their ability to form stable transition metal complexes and to modify reactivity through both sterics and electronics. A very large number of chiral phosphine ligands have been prepared, although only a small portion of them have gained popular use. A representative sampling of some of the common chiral phosphine ligand designs that have been investigated are shown below.

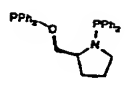
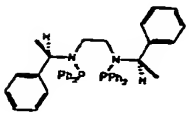
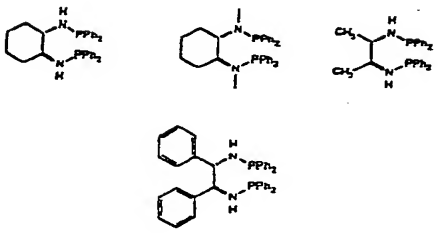
Prior Art

Ligand	Structure	Citing Reference
1		Morrison et al., *J. Org. Chem.*, 1974, *39*, 270

	2		Masuda et al., *J. Am. Chem. Soc.*, 1978, *100*, 268
5	3		LaFont et al., *J.Chem. Research (S)*, 1982, 117
	4		Riley, *J. Organomet. Chem.*, 1982, *234*, 85
10	5		MacNeil et al., *J. Am. Chem. Soc.*, 1981, *103*, 2273
	6		Fryzuk et al., *J. Am. Chem. Soc.*, 1977, *99*, 6262
15	7		Wild et al., *J. Am. Chem. Soc.*, 1979, *101*, 6254
	8		Bergstein et al., *Synthesis*, 1981, *76*
20	9		Juge et al., *Tetrahedron Lett.*, 1990, *31*, 6357
25	10		Imamoto et al., *J. Am. Chem. Soc.*, 1990, *112*, 5244
	11		Knowles et al., *J. Am. Chem. Soc.*, 1975, *97*, 2567
30	12		Takaya et al., *Tetrahedron Lett.*, 1990, *31*, 7185
	13		LaFont et al., *J.Chem. Research (S)*, 1982, 117
35	14		Achiwa, *J. Am. Chem. Soc.*, 1976, *98*, 8265

15		Beck et al., *J. Organomet. Chem.*, 1977, *133*, 307
16		Kagan et al., *J. Am. Chem. Soc.*, 1972, *94*, 6429
17		Anviron-Violet et al., *J. Mol. Catal.*, 1979, *5*, 41
18		Dang et al., *J. Organomet. Chem.*, 1975, *91*, 105
19		Glaser et al., *Tetrahedron Lett.*, 1977, 4639
20		Kreuzfeld et al., *React. Kinet. Catal. Lett.*, 1981, *16*, 229
21		Pracejus et al., *J. Mol. Catal.*, 1984, *24*, 227
22		Samuel et al., *Nouv. J. Chim.*, 1981, *5*, 15
23		Lauer et al., *J. Organomet. Chem.*, 1979, *177*, 309
24		Tanaka et al., *Chem. Lett.*, 1975, 1115
25		Alario et al., *J. Chem. Soc., Chem. Comm.*, 1986, 202

26		Takaya et al., *Org. Syn.*, 1989, *67*, 20
27		Grubbs et al., *Tetrahedron Lett.*, 1977, *26*, 1879
28		Trost et al., *Organometallics*, 1985, *4*, 1143
29		Tamao et al., *Tetrahedron Lett.*, 1977, *16* 1389
30		Miyano et al., *Chem. Lett.*, 1980, 729
31		Miyano et al., *Bull. Chem. Soc. Jpn.*, 1984, *57*, 2171
32		Uehara et al., *Chem. Lett.*, 1983, 441
33		Hayashi et al., *Bull. Chem. Soc. Jpn.*, 1980, *53*, 1138
34		Hayashi et al., *Acc. Chem. Res.* 1982, *15*, 395
35		Johnson et al., *J. Mol. Catal.*, 1981, *12*, 37

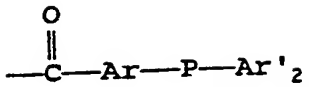
36		Petit et al., *Nouv. J. Chim.*, 1983, *7*, 593
37		Pracejus et al., *Tetrahedron Lett.*, 1977, *39*, 3497
38		Fiorini et al., *J. Mol. Catal.*, 1978, *4*, 125; Fiorini et al., *J. Mol. Catal.*, 1979, *5*, 303; and Onuma et al., *Chem. Lett.*, 1979, 905

Enantiodiscrimination between 1-cyclopenten-3,5-diol derivatives is directly applicable to the synthesis of prostanoids (see Kitamura et al., "Kinetic Resolution of 4-Hydroxy-2-cyclopentenone by Rhodium Catalyzed Asymmetric Isomerization", *Tetrahedron Lett.*, 1987, *28*, 4719) and carbanucleosides that are potential anti-viral and anti-tumor compounds (such as carbovir and aristeromycin, the latter discussed by Trost et al., *J. Am. Chem. Soc.*, 1988, *110*, 621 (1988).

Summary of the Invention.

It is an object of the present invention to provide a new class of ligands that are useful for transition metal catalyzed bond forming reactions.

In one aspect of the present invention, a ligand is provided that is useful for transition metal catalyzed bond forming reactions and comprises a metal binding portion bound to a chiral scaffold. The chiral scaffold is derived from an asymmetric alcohol or an asymmetric amine. The metal binding portion has at least one metal binding moiety with the structure



wherein Ar and Ar' each is an aryl or a heteroaryl with a single ring or fused rings. The metal binding portion and the chiral scaffold are preferably bound with two or three metal binding moieties for each chiral scaffold. The chiral scaffold preferably is a C_2 symmetric diol or diamine.

In another aspect of the present invention, a method for preparing ligands useful for transition metal catalyzed bond forming reactions comprises providing an aromatic carboxylic acid having a diarylphosphino or diheteroarylphosphino substituent on the aromatic ring, and forming an ester or an amide derivative of the carboxylic acid by coupling with a chiral diol or a chiral diamine in the presence of dicyclohexyl-carbodiimide.

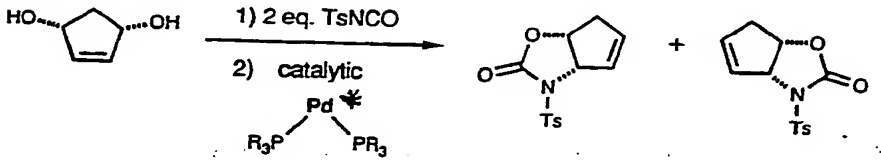
In a further aspect of the present invention, a method for synthesizing cyclopentane analogs of carbohydrates comprises asymmetrically introducing heteroatoms around a cyclopentane nucleus of an intermediate while controlling the introduction by inducing an enantiomeric excess. Control is exercised by contacting the intermediate with a transition metal and a ligand for the transition metal. The ligand has a metal binding portion bound to a chiral scaffold. The chiral scaffold is derived from an asymmetric alcohol or an asymmetric amine. The metal binding portion is an aryl carboxylic acid derivative or a heteroaryl carboxylic acid derivative with a diarylphosphino or diheteroaryl-phosphino substituent on the aryl or on the heteroaryl moiety. The chirality of the ligand may be selected so as to correspond to the desired absolute stereochemistry induced in the transition metal catalyzed reaction.

Ligands of the invention can be easily and flexibly prepared over a broad spectrum of chiral scaffolds for high levels of asymmetric induction. Inventive ligands preferably contain a plurality of metal binding sites and are capable of forming C_2 symmetrical complexes. Among the inexpensive and readily available chiral diols useful for derivatizing 2-diphenylphosphinobenzoic acid to prepare ligands in accordance with the invention are mannitol and tartaric acid, with particularly effective ligands prepared from chiral diamines.

Detailed Description of the Preferred Embodiments.

Many ligands in accordance with the present invention give enantiomeric excesses ("e.e.") of about 75% or greater when tested in a relatively difficult transition metal catalyzed bond forming, five membered ring reaction. This e.e. test involves the ability of a chiral ligand to participate with palladium in a catalysis illustrated by Reaction 1 below.

REACTION 1



(* Present in a catalytic amount)

Unless otherwise indicated, the enantiomeric excesses obtained and reported herein will have been obtained with the cyclopentene diol substrate illustrated by Reaction 1. However, we have also obtained enantiomeric excesses through use of the inventive ligands in bond forming reactions involving six and seven membered rings

up to almost 100% (that is, obtaining reaction products that are substantially optically pure).

Transition metal catalyzed bond forming reactions (with which ligands in accordance with the invention are useful) are well known in the art, and among the recent reviews describing such reactions are:

(1) Consiglio et al., "Enantioselective Homogeneous Catalysis Involving Transition-Metal-Allyl Intermediates", *Chem. Rev.*, 1989, *89*, 257-276;

(2) Noyori et al., "Enantioselective Catalysis with Metal Complexes. An Overview." *Modern Synthetic Methods, Vol. 5*, Scheffold, ed., Springer-Verlag: Berlin, 1989, 115-198;

(3) Noyori, R., "Chemical Multiplication of Chirality: Science and Applications," *Chem. Soc. Rev.*, 1989, *18*, 187-208;

(4) Ojima et al., "Recent Advances in Catalytic Asymmetric Reasons Promoted by Transition Metal Complexes", *Tetrahedron*, 1989, *45*, 6901-6939;

(5) Blystone, S.L., "Synthetic Applications of Enantioselective Organotransition-Metal-Mediated Reactions," *Chem. Rev.*, 1989, *89*, 1663-1679;

(6) Brunner, H.T., "Enantioselective Synthesis with Optically Active Transition Metals," Chapter 4 in *The Chemistry of the Metal-Carbon-Bond, Vol. 5*, Hartley, ed., John Wiley & Sons: New York, 1989, 109-146;

(7) Brunner, H.T., "Enantioselective Synthesis with Optically Active Transition Metal Catalysts," *Synthesis*, 1988, 645-654; and

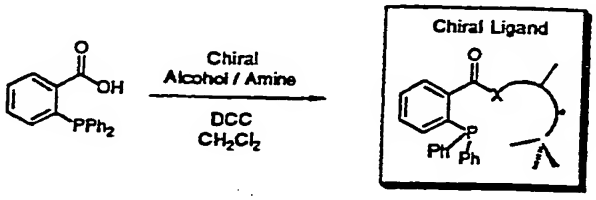
(8) Merlic, C.A., "Ch. 3. Transition Metal-Mediated Asymmetric Allylic Alkylations," *Molybdenum Catalyzed Allylic Alkylations*, Ph.D., University of Wisconsin, Madison, 1988, pp. 78-79.

Among such transition metal catalyzed bond forming reactions are those involving palladium. One

application of this invention is to form cyclopentane analogs of carbohydrates through use of the inventive ligands and palladium. Preparation of mannostatin A exemplifies this class. Particularly preferred asymmetric ligands of the invention for transition metal catalyzed reactions are derived from 2-diphenylphosphinobenzoic acid (2-DPPBA) as ester or amide derivatives of chiral alcohols and chiral amines.

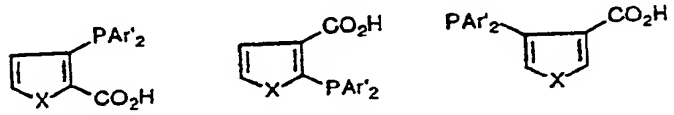
The 2-DPPBA may be derivatized with any of a wide variety of chiral alcohols or chiral amines, preferably by coupling in the presence of dicyclohexylcarbodiimide (DCC), as illustrated by Reaction 2.

REACTION 2

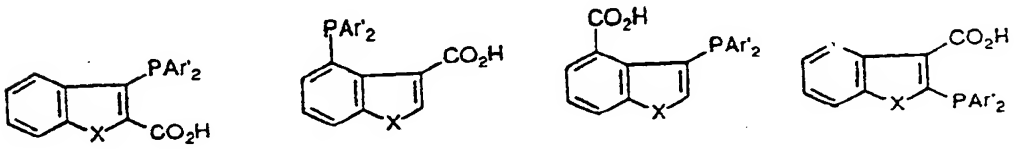


While a derivatized 2-DPPBA is a particularly preferred manner of practicing the present invention, with 2-DPPBA forming the metal binding moiety of the inventive ligand, other aromatic carboxylic acids can be used so long as the aromatic carboxylic acid carries a diarylphosphino (or a diheteroarylphosphino) substituent. Thus, the necessary phosphino substituent and the carbonyl substituent may be on an aryl or heteroaryl that is further substituted by a moderately or weakly activating or deactivating group, such as with an alkyl group (branched or unbranched) usually with not greater than about ten carbons, a halide, or an alkoxy (e.g., —OCH_3, —OC_2H_5, etc.). Alternatively, the single aryl ring exemplified by 2-DPPBA can be replaced with a fused aryl or heteroaryl ring, such as, for example, naphtha-

lene (optionally substituted as just described for the single aryl ring). In such an instance of fused rings, the necessary phosphino substituent and the carboxyl substituent can either be 1,2 on the one ring or can be 1,3 across the two rings. Among the heteroatoms that can form the single or fused heteroaryl ring of the aromatic carboxylic acid from which the inventive ligands may be derived are nitrogen, oxygen, and sulfur. Illustrative, suitable heteroaryl carboxylic acids on which the diarylphosphino (or diheteroarylphosphino) group can be substituted include compounds such as



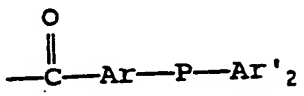
X = O, S, NR



As is illustrated by the preferred embodiment derived from 2-DPPBA, the carboxyl group and the diphenylphosphino group are preferably in an ortho relationship, which serves best for the ligand function.

Thus, to summarize, ligands of the invention have metal binding portion that is bound to a chiral scaffold. The metal binding portion has at least one metal binding moiety (preferably two and sometimes three) with the Formula 1 structure:

FORMULA 1



wherein Ar and Ar' each is an aryl or a heteroaryl with a single ring or fused rings. An illustrative heteroaryl for Ar' is, for example, 2-furyl. The "PAr'_2" moiety will sometimes hereinafter be referred to as an "aromatic phosphino."

When the chiral scaffold is derived from an alcohol, then it and the metal binding portion will be bound through an ester linkage. When the chiral scaffold is derived from an amine, then it and the metal binding portion will be bound through an amide linkage. That is, the metal binding portion (or portions) and the chiral scaffold are preferably covalently bound.

A great number of chiral alcohols and chiral amines are suitable for coupling with the aryl or heteroaryl carboxylic acid. We have found it most convenient to conduct the coupling reaction in the presence of DCC because our attempts with alternate strategies have frequently led to the formation of tar. We have also found that the DCC coupling reaction when using alcohols is sensitive to steric hindrance of the reacting alcohol. Thus, primary or secondary alcohols are preferred when a chiral alcohol is selected. Table 1 summarizes a variety of inventive embodiments.

TABLE 1

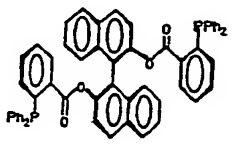
Inventive Ligand Embodiment	Structure of the Ligand	e.e. from Reaction 1
(+)-6.24		40%

TABLE 1 (cont.)

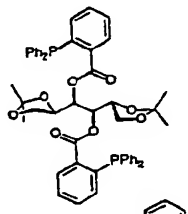
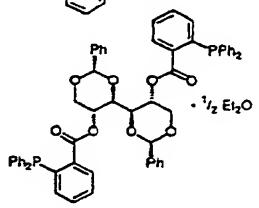
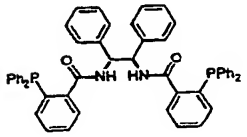
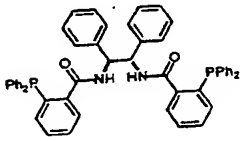
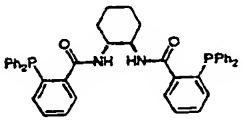
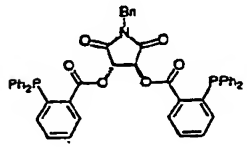
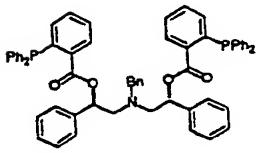
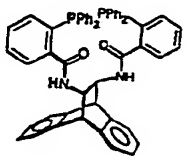
Inventive Ligand Embodiment	Structure of the Ligand	e.e. from Reaction 1
(+)-6.25		64%
(-)-6.26		61%
(+)-6.27		80%
(-)-6.27		79%
(-)-6.28		78%
(+)-6.29		75%
(-)-6.31		60%

TABLE 1 (cont.)

Inventive Ligand Embodiment	Structure of the Ligand	e.e. from Reaction 1
(+)-6.32		88.1%

Our earlier ligand designs had involved the use of acyclic diols to give ligands exemplified by ligands 6.24 and 6.24 (as designated in Table 1). More rigid chiral cyclic diols, such as the ligand derived from the benzyltartriimide, led to even better enantiomeric excess (ligand embodiment 6.29). This is a particularly preferred ligand embodiment from diols because it is derived from the inexpensive and readily available tartaric acid. In general, however, the bis-amide ligands give better e.e. than the bis-esters. We attribute these results to the rigidity of the amide linkage, which tends to freeze rotational freedom at the carbonyl-heteroatom bond.

The invention will now be further illustrated by the following examples describing the preparation of ligand embodiments summarized in Table 1. Example A exemplifies the (known) preparation of the particularly preferred carboxylic acid precursor, 2-DPPBA. Examples B and C give two alternate general procedures for the preparation of ligands from the 2-DPPBA in a coupling using DCC. Examples 1-8 describe in detail the preparations of the ligands summarized in Table 1. The remaining examples then illustrate some uses of the inventive ligands.

EXAMPLE A

Preparation of 2-Diphenylphosphinobenzoic acid, 2-DPPBA.

To a 100 mL recovery flask equipped with a reflux condenser containing methyl-2-iodobenzoic acid (4.468 g, 17.05 mmol) under nitrogen was added bis(benzonitrile)palladium dichloride (97.5 mg, 0.254 mmol) followed by anhydrous benzene (34 mL). Trimethylsilyldiphenylphosphine (4.50 mL, 6.17 g, 23.9 mmol) was added and the mixture was stirred at 60°C for 29 h. More trimethylsilyldiphenylphosphine (1 mL, 1.38 g, 5.34 mmol) was added and stirring was continued at 60°C for 19 h.

Anhydrous methanol was added (to react with TMSI) and solvent was removed *in vacuo*. To the residual mixture was added absolute ethanol (25 mL), water (10 mL), and potassium hydroxide (2.909 g, 51.84 mmol). The mixture was stirred under nitrogen at 80°C for 2.5 h and then allowed to cool to room temperature. Solvent was removed *in vacuo* and the mixture was taken up in water and washed with ether to remove neutral impurities (discarded the ether layer). The aqueous layer was acidified to pH<1 with concentrated hydrochloric acid and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and solvent was removed *in vacuo*. The residual solid was adsorbed onto a minimum amount of silica gel. The silica gel was loaded onto a 4.3x14 cm column of silica gel and eluted with 50% ethyl acetate/hexanes (1 L) followed by 70% ethyl acetate/hexanes (500 mL).

A small amount of baseline material (TLC) contaminated the product, so the solid was taken up in hot ether (100 mL) and hexanes (ca. 175 mL) was added with gentle warming till the solution became slightly cloudy. Crystallization occurred upon slow cooling

under nitrogen to afford 2-diphenylphosphinobenzoic acid as yellow crystals (2.775 g, 53.1%).

EXAMPLE B

General Procedure A for the preparation of ligands with 2-diphenylphosphinobenzoic acid using DCC.

To a dry flask containing alcohol or amine, excess 2-diphenylphosphinobenzoic acid, 5 mol% 4-dimethylaminopyridine and dicyclohexylcarbodiimide under nitrogen was added anhydrous solvent (THF or dichloromethane). The resultant yellow chalky mixture was stirred at room temperature until thin layer chromatography indicted complete reaction.

The reaction mixture was filtered through a 2 cm pad of celite (wetted with dichloromethane) and the filter cake was washed twice with an equal volume of dichloromethane. Solvent was removed *in vacuo* and the residue was chromatographed on silica gel.

EXAMPLE C

General Procedure B for the preparation of ligands with 2-diphenylphosphinobenzoic acid using DCC.

To a dry flask containing alcohol or amine, excess 2-diphenylphosphinobenzoic acid, 5 mol% 4-dimethylaminopyridine in anhydrous solvent (THF or dichloromethane) under nitrogen was added dicyclohexylcarbodiimide. The yellow, chalky mixture was stirred at room temperature until thin layer chromatography indicted complete reaction.

The reaction mixture was filtered through a 2 cm pad of celite (wetted with dichloromethane) and the filter cake was washed twice with an equal volume of dichloromethane. Solvent was removed *in vacuo* and the residue was chromatographed on silica gel.

EXAMPLE 1

(S)-(+)-Bis-[2-(diphenylphosphino)benzoyl]-1,1'-binaphthol, 6.24.

(Procedure B) -- The reaction was run with S-(-)-1,1'-binaphthol (96.8 mg, 0.338 mmol), 2-diphenylphosphinobenzoic acid (226.5 mg, 0.740 mmol), and dicyclohexylcarbodiimide (0.167 g, 0.809 mmol) in dichloromethane (1.5 mL) for 8 h.

The residue was chromatographed on a 2x11 cm column of silica gel with 15% ethyl acetate/hexanes to give the diester, as a white solid (193.5 mg). The solid was recrystallized from hot dichloromethane/hexanes to give the diester, (S)-BDPPB, 6.25, as white needles (160 mg, 54.9%).

Ligand (S)-(+)-6.24: white needles from dichloromethane/hexane), m.p. 114-116°C.

R_f 0.55 (30% ethyl acetate/hexanes).

IR (neat film from $CDCl_3$) 3069, 3056, 3016, 3002, 2932, 2855, 1955(w), 1901(w), 1817(w), 1731(s), 1585, 1511, 1478, 1463, 1434, 1267, 1245, 1220, 1206, 1137, 1089, 1043, 908, 807, 742, 696, 649 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz) δ 7.89(d, J=8.9Hz, 2H), 7.85(d, J=7.9Hz, 2H), 7.38(6d, J=6.9, 1.2Hz, 2H), 7.08-7.30(m, many H), 7.06 (ddd, J=7.9, 3.7, 1.3Hz, 2H), 6.98(td, J=7.5, 1.1Hz, 2H), 6.75(ddd, J=6.9, 4.0, 1.2Hz, 2H), 1.55(H_2O).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.31, 146.73, 141.03(d, J=27.5Hz), 137.92(d, J=11.2Hz), 137.62(d, J=11.7Hz), 134.02, 133.88, 133.82, 133.75, 133.69, 133.61, 133.41, 133.16, 132.66, 132.49, 131.91, 131.36, 130.78, 129.24, 128.55, 128.45, 128.37, 128.28, 127.73, 126.79, 125.89, 125.55, 123.41, 121.88.

Anal. Calcd. for $C_{58}H_{40}O_4P_2 \cdot 0.67H_2O$: C:79.62; H:4.76; Found: C:79.64; H:4.85 and C:79.58; H:5.08.

$[\alpha]_D$=+55.44(±.55)°(c1.11, dichloromethane).

EXAMPLE 2

(+)-1,2:5,6-Di-O-isopropylidene-3,4,-bis-O-(2'-diphenylphosphinobenzoyl)-D-mannitol, 6.25:

(Procedure B) -- The reaction was run with (+)-1,2:5,6-di-O-isopropylidene-D-mannitol (0.105 g, 0.400 mmol, Aldrich), 2-diphenylphosphinobenzoic acid (0.269 g, 0.878 mmol), and dicyclohexylcarbodiimide (0.206 g, 0.966 mmol) in dichloromethane (1.4 mL) for 11 h.

The residue was chromatographed on a 2x13 cm column of silica gel with 10% ethyl acetate/hexanes to give the diester 6.25 as a clear oil (44.3 mg, 13.2%).

Ligand 6.25: clear oil.

R_f 0.83 (60% ethyl acetate/hexanes).

IR (neat film from $CDCl_3$) 3070, 3055, 2987, 2935, 2890, 1724(s), 1585, 1478, 1463, 1434, 1381, 1372, 1245(s), 1139, 1245(s), 1139, 1101, 1066, 1054, 909, 850, 745, 697 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) δ 8.15(m, 2H), 7.18-7.42(m, 24H), 6.94(m, 2H), 5.47(dt, J=6.0, 1.1Hz, 2H), 4.07(q, J=6.1Hz, 2H), 3.68(dd, J=8.5, 6.1Hz, 2H), 3.59(dd, J=8.6, 6.5Hz, 2H), 1.21(s, 6H), 1.20(s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.46, 165,40, 141.71(d, J=28.8Hz), 137.97(d, J=12.3Hz), 134.53, 134.18(d, J=20.6Hz), 134.06(d, J=21.0Hz) 133.30(d, J=18.1Hz), 132.50, 131.24, 128.811, 128.69, 128.55, 128.43, 109.30, 74.41, 72.40, 65.82, 26.18, 24.96.

$[\alpha]_D$=+55.45(±.15)°(c4.29, dichloromethane).

HRMS: calc'd for $C_{50}H_{48}O_8P_2$-CH_3: 823.2590.

Found: 823.2590.

FAB MS: Calc'd for $C_{50}H_{49}O_8P_2$ ($M+H^+$): 839.2903.

Found: 839.2916.

EXAMPLE 3

(−)-1,3:4,6-Di-O-benzylidene-D-mannitol, bis-[2-diphenylphosphinobenzoate], hemietherate complex, 6.26.

(Procedure A) -- The reaction was run with 1,3:4,6-di-O-benzylidene-D-mannitol (272 mg, 0.759 mmol), 2-diphenylphosphinobenzoic acid (0.5345 g, 1.745 mmol), and dicyclohexylcarbodiimide (0.396 g, 1.92 mmol) in THF (5.5 mL) for 25 h.

The residue was chromatographed on a 2x12 cm column of silica gel with 5-10% ether/hexanes to afford impure product. The impure product was mixed with hot ether and dichloromethane was added with swirling until the mixture became homogeneous. The solution was stored in a refrigerator (7°C) allowing the formation of diester 6.26 as clear plates. The crystallization was repeated once more for a total yield of 0.342g (46.4%) for the 2 crops. The product holds 0.5 mol ether of crystallization tenaciously.

Ligand 6.26: m.p. 125-127°C (plates from ether/dichloromethane).

R_f 0.59 (30% ethyl acetate/hexanes).

IR (neat film from $CDCl_3$) 3069, 3056, 2866, 1955(w), 1890(w), 1815(w), 1722(s), 1585, 1478, 1463, 1435, 1377, 1312, 1266, 1249, 1224, 1140, 1111, 1058, 1027, 998, 909, 745, 731, 690 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ8.16(dd, J=7.7, 3.7Hz, 2H), 7.1-7.5(m, H), 6.92(dd, J=7.8, 3.9Hz, 2H), 5.49(ddd, J=9.8, 9.2, 5.3Hz, 2H), 5.24(s, 2H), 4.215(d, J=10.4, 5.5Hz, 2H), 4.10(d, J=9.5Hz, 2H), 3.48(q, J=7.0Hz, 2H, etherate), 3.23(t, J=10.4Hz, 2H), 1.21(t, J=7.0Hz, 3H, etherate).

^{13}C NMR ($CDCl_3$, 50 MHz) δ165.49 (d, J=2.6Hz), 140.51(d, J=7.4Hz), 137.98, 137.88, 137.77, 137.65, 137.28, 134.60, 134.18, 133.90, 133.73, 133.51, 133.34, 132.59,

131.30, 129.02, 128.79, 128.72, 128.65, 128.1-5(m), 128.02, 126.23, 100.87, 75.62, 67.30, 62.24.
$[\alpha]_D$=-47.83(±0.39)°(c1.68, dichloromethane).
Anal. Calc'd for $C_{58}H_{48}O_8P_2$: C,74.51; H,5.17.
Found: C,74.37; H,5.55.

EXAMPLE 4A

(-)-1R,2R-bis(2'-diphenylphosphinobenzamido)-1,2-diphenylethane, 6.27.

(Procedure B) -- The reaction was run with (+)-1R, 2R-diphenylethanediamine (0.338 g, 1.59 mmol, $[\alpha]_D$=+103.0(±.8)°(c1.115, methanol),2-diphenylphosphinobenzoic acid (1.024 g, 3.343 mmol), and dicyclohexylcarbodiimide (0.720 g, 3.493 mmol) in dichloromethane (10 mL) for 4 h.

The residue was chromatographed on a 4x11 cm column of silica gel with 1:3 ether/hexanes (100 mL) then 30% ethyl acetate/hexanes (400 mL) followed by 50% ethyl acetate/hexanes (200 mL) to elute the diamide 6.27 as a glass (0.798 g, 63.5%).

Ligand (-)-6.27: white solid precipitated from dichloromethane with hexanes, m.p. 135-136°C.
R_f 0.61 (60% ethyl acetate/hexanes).
IR (neat film from $CDCl_3$) 3410, 3326(b), 3071, 3046, 2979, 2937, 2873, 1956(w), 1889(w), 1818(w), 1733, 1653(s), 1586, 1564, 1514(s), 1459, 1154, 1122, 1091, 1071, 1046, 1028 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz) δ 7.64(m, 2H), 7.15-7.35(m, 16H), 7.05-7.15(m, 16H), 6.88-6.93(m, 6H), 5.37(m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.20, 140.53(d, J=24.5Hz), 138.40, 137.69(d, J=12.2Hz), 137.34(d, J=12.0Hz), 136.77(d, J=22.4Hz), 134.34, 133.87(d, J=20.5Hz), 133.67(d, J=21.2Hz), 130.28, 128.70, 128.48, 128.39, 128.33(b,>1 signal), 127.91, 127.86, 127.63, 127.49, 59.60.

Analysis Calcd. for $C_{52}H_{42}N_2O_2P_2$: C,79.17; H,5.37; N,3.55; P,7.85. Found: C,79.17; H,5.37;N,3.50; P,8.24. $[\alpha]_D$=-27.5(±.5)°(c1.63, dichloromethane).

EXAMPLE 4B

(+)-1S,2S-bis(2'-diphenylphosphinobenzamido)-1,2-diphenylethane, 6.27.

(Procedure B) - The reaction was run with (-)-1S, 2S-diphenylethanediamine (0.338 g, 1.59 mmol, $[\alpha]_D$=+104.0°(c1.09, methanol),2-diphenylphosphinobenzoic acid (1.024 g, 3.343 mmol), and dicyclohexylcarbodiimide (0.720 g, 3.493 mmol) in dichloromethane (10 mL) for 6 h.

The residue was chromatographed on a 4x11 cm column of silica gel with 1:3 ether/hexanes (100 mL) then 30% ethyl acetate/hexanes (400 mL) followed by 50% ethyl acetate/hexanes (200 mL) to elute the diamide 6.27 as a glass (0.980 g, 78.0%).

Ligand (+)-6.27: white solid precipitate from dichloromethane with hexanes.

R_f 0.61 (60% ethyl acetate/hexanes).

$[\alpha]_D$=+27.4(±.6)°(c1.62, dichloromethane).

EXAMPLE 5

(-)-1R,2R-Diamino-1N,2N-bis(2'-diphenylphosphinobenzoyl) cyclohexane, 6.28.

(Procedure B) - The reaction was run with (-)-1R, 2R-diaminocyclohexane (0.1312 g, 1.149 mmol, Aldrich), 2-diphenylphosphinobenzoic acid (0.774 g, 2.528 mmol), and dicyclohexylcarbodiimide (0.521 g, 2.528 mmol) in dichloromethane (4 mL) for 9 h.

The residue was chromatographed twice on silica gel with 15-30% ethyl acetate/hexanes (gradient)

to give the diamide 6.28 as a glass foam (0.2366 g, 29.8%).

Ligand 6.28: waxy solid precipitated from dichloromethane with hexanes, m.p. 80-120°C.

R_f 0.43 (50% ethyl acetate/hexanes).

IR (neat film from $CDCl_3$) 3303, 3070, 2935, 2857, 1955(w), 1887(w), 1817(w), 1645(s), 1538, 1478, 1434, 1328, 1306, 1162, 1091, 909 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) δ 7.57(m, 2H), 7.15-7.26(m, 24H), 6.91(m, 2H), 6.31(bd, J=7.7Hz, 2H, N-H), 3.77(m, 2H), 1.87(m, 2H), 1.62(m, 2H), 0.9-1.3(m, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.46, 140.80(d, J=24.2Hz), 137.96(d, J=11.8Hz), 137.88(d, J=12.3Hz), 136.81(d, J=21.6Hz), 134.34, 133.97(d, J=20.3Hz), 130.23, 128.79, 128.66, 128.57, 128.51, 128.43, 127.63, 127.55, 53.68, 31.71, 24.41.

Analysis calcd. for $C_{44}H_{40}N_2O_2P_2$: C,76.51; H,5.83; N,4.06; P,8.97. Found: C,76.16; H,6.28; N,4.02; P,8.93.

$[\alpha]_D$=-46.7(±.3)°(c2.366, dichloromethane).

EXAMPLE 6

(+)-1R,2R-N-benzyl-2O,3O-bis(2'-diphenylphosphinobenzoyl)tartrimide, 6.29.

(Procedure A) - The reaction was run with (+)-1R, 2R-N-benzyltartrimide (0.303 g, 1.37 mmol), 2-diphenylphosphinobenzoic acid (0.922 g, 3.018 mmol), and dicyclohexylcarbodiimide (0.649 g, 3.45 mmol) in THF (5 mL) for 24 h.

The residue was chromatographed on a 2.5x13 cm column of silica gel with 10-20% ethyl acetate/hexanes (gradient) to afford ligand 6.29 as an oil (0.88 g, 70.4%).

Ligand (+)-6.29: clear oil.

R_f 0.36 (1:1 ether/hexanes).

IR (neat film from $CDCl_3$) 3056, 3070, 2935, 1955(w), 1888(w), 1804(w), 1730(s), 1586, 1479, 1463, 1435, 1399, 1350, 1332, 1271, 1249, 1171, 1138, 1105, 1069, 1037, 998, 909 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) δ 8.03(m, 2H), 7.13-7.45(m, 29H), 6.92(m, 2H), 4.73(d, J=14.2Hz, 1H), 4.58(d, J=14.2Hz, 2H).

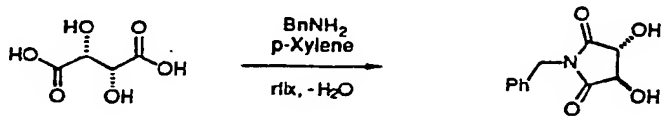
^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.94, 165.54, 141.63(d, J=28.8Hz), 137.66(d, J=11.2Hz), 137.39(d, J=11.6Hz), 134.72, 134.46, 134.16(d, J=20.9Hz), 134.00(d, J=20.7Hz), 132.96, 132.17(d, J=18.6Hz), 131.75, 131.72, 128.94(br), 128.81, 128.77, 129.19(d, J=4.6Hz), 128.56, 128.36, 128.23, 73.03, 42.81.

$[\alpha]_D$=+77.5(±.3)°(c1.025, dichloromethane).

Anal. calc'd for $C_{49}H_{37}NO_6P_2$: C,73.77; H,4.67.
Found: C,73.50; H,5.01.

The ligand 6.29 is a particularly preferred embodiment of the invention when prepared from chiral diols because the chiral diol useful as the chiral scaffold in preparing inventive ligand 6.29 is readily derived from tartaric acid via tartrimide. Preparation of the tartrimide from tartaric acid is known and is generally illustrated by Reaction 3 as follows:

REACTION 3



The ligand 6.29 can have Bn as aryl or alkyl (such as, for example, lower alkyl) in addition to benzyl.

EXAMPLE 7

(-)-3-aza-3-benzyl-1R, 5R-dihydroxy-10, 50-bis(2'-diphenylphosphinobenzoyl)-1, 5-diphenylpentane, 6.31.

(Procedure B) -- The reaction was run with 3-aza-3-benzyl-1R, 5R-dihydroxy-1, 5-diphenylpentane (0.223 g, 0.642 mmol), 2-diphenylphosphinobenzoic acid (0.413 g, 1.348 mmol), and dicyclohexylcarbodiimide (0.285 g, 1.38 mmol) in dichloromethane (3 mL) for 36 h.

The residue was chromatographed on a 2.5x14 cm column of silica gel with 5% ethyl acetate/hexanes and then rechromatographed with 5:20:75 ethylacetate/chloroform/hexanes to afford ligand 6.31 as a glass oil (0.179 g, 30.2%).

Ligand (+)-6.31: glass oil.

R_f 0.60 (30% ethyl acetate/hexanes).

IR (neat film from $CDCl_3$) 3066, 3031, 2957, 2929, 2830, 1952(w), 1882(w), 1813(w), 1716(s), 1586, 1495, 1478, 1463, 1455, 1434, 1361, 1310, 1268, 1252, 1141, 1106, 1057, 1027, 1002, 965, 909 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ 8.05(m, 2H), 6.85-7.4(m, 34H), 5.90(t, J=6.6Hz, 2H), 3.68(d, J=4.0Hz, 2H), 3.47(d, J=4.0Hz, 2H), 2.84(m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.98, 140.85, 140.81, 139.23, 138.83, 138.35, 138.18, 138.01, 134.66, 134.44, 134.28, 134.23, 134.01, 133.96, 132.03, 130.98, 128.85, 128.68, 128.59, 128.50, 128.28, 128.17, 128.07, 127.89, 127.79, 127.17, 127.07, 126.73, 74.3, 58.98, 58.52.

$[\alpha]_D$=-5.04(±.4)°(c1.79, dichloromethane).

LSIMS: mle 924 (M^+ + H,55), 618(76), 528(100).

EXAMPLE 8

(+)-11S,12S-bis(2'-diphenylphosphinobenzamido)-9,10-dihydro-9,10-ethanoanthracene, 6.32.

(Procedure B) -- The reaction was run with (+)-11S,12S-diamino-9,10-dihydro-9,10-ethanoanthracene (0.253 g, 1.071 mmol, $[\alpha]_{405}$ =+81.3° (c 2.275, methanol)), 2-diphenylphosphinobenzoic acid (0.6887 g, 2.248 mmol), and dicyclohexylcarbodiimide (0.463 g, 2.248 mmol) in dichloromethane (5 mL) for 10 h.

The residue was chromatographed on a 4.5x11.5 cm column of silica gel with 900 mL 30% ethyl acetate/hexanes to give diamide 6.32 as a glass foam (0.860 g, 98.8%).

Ligand (+)-6.32: glass foam.

R_f 0.63 (50% ethel acetate/hexanes).

IR (neat film from $CDCl_3$) 3418, 3396, 3305(b), 3070, 3063, 3026, 1955(w), 1905(w), 1885(w), 1818(w), 1652(s), 1585, 1505(s), 1480, 1459, 1327, 1308, 1293, 1250, 1228, 1155, 1124, 1090, 1027, 909 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) δ 7.0-7.45(m, 34H), 6.95(m, 2H), 5.72(bd, J=6.8Hz, 2H, N-H), 4.42(d, J=2.4Hz, 2H), 3.94(m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.00, 141.17(d, J=26Hz), 141.028, 136.76(d, J=12Hz), 137.36(d, J=11.6Hz), 136.45(d, J=21.5Hz), 134.54, 133.95(d, J=20.3H), 133.79(d, J=20.2Hz), 130.36, 128.88, 128.79, 128.74, 128.65, 128.63, 127.60(d, J=5.1Hz), 126.75, 126.64, 126.03, 124.83.

Analysis calcd. for $C_{54}H_{42}N_2O_2P_2$: C, 79.79; H 5.21; N, 3.45. Found: C, 80.01; H 5.28; N, 3.36.

$[\alpha]_{405}$=+211.2(±.3)°(c3.35, 26°C, dichloromethane).

$[\alpha]_{477}$=+84.7(±.3)°(c3.35, 25°C, dichloromethane).

The enantiomeric excesses obtained with the inventive ligands 6.24 and 6.25 are quite good (up to 64% e.e. for ligand 6.25), with the ligand 6.29 (which is believed to have a further restricted number of degrees of freedom) having a 75% enantiomeric excess. The amides gave even better enantiomeric excesses (about 80-88% e.e.) and are particularly preferred embodiments of the invention.

We have found that C_2-symmetrical complexes (that is, the ligands which bind palladium with C_2 symmetry) give high orders of enantioselectivity and also permit predictable enantiomeric formation. That is, we have found that the ligand stereochemistry predicts product stereochemistry. Thus, while the stereogenic backbone of the inventive ligands has no direct interaction with the palladium-olefin moiety, the two otherwise independent triphenylphosphines defined by the chiral linkage, or scaffold, serve to organize the aromatic rings into a chiral array and provide a direct relationship for absolute stereochemistry of the product from the catalysis.

Example 9 illustrates a general procedure for palladium catalysis with inventive ligands exemplified by chiral 2-(diphenylphosphino)benzoate esters and amides.

EXAMPLE 9

(Scalemic)-1-p-toluenesulfonylcyclopent-5-eno[4,3-d]-3aS, 6aR-oxazolidin-2-one.

To a flask containing a 1M solution of 1R,4S-dihydroxycyclopent-2-ene in anhydrous THF under nitrogen was added p-toluenesulfonylisocyanate (205 mol%) dropwise resulting in an exothermic reaction. The solution was stirred at 50°C for 1 h.

A dry flask was charged with an inventive chiral ligand (15-20 mol% for monodentate and 7.5 mol% for bidentate ligands) and tris(dibenzylideneacetone)dipalladium(0)chloroform complex (2.5 mol%) under nitrogen and anhydrous THF was added. The black-purple slurry was stirred at room temperature until a homogeneous solution was obtained and then at 50°C for 10 minutes resulting in a clear, red-orange solution (0.05M in palladium). The catalyst solution was then cooled to 0°C and the bis-carbamate solution was added dropwise. The reaction was stirred at 0°C until thin layer chromatograph. (50% ethyl acetate/hexanes) indicated complete consumption of bis-carbamate and then solvent was removed *in vacuo*. The resulting brown-orange oil was directly chromatographed on silica gel with 10-20% ethyl acetate/hexanes (gradient) to afford scalemic oxazolidinone.

The Example 9 procedure was used for each of the inventive ligands reported in Table 1 for product yields up to 100% (through use of ligand 6.25 and ligand 6.31). Inventive ligands were used in the asymmetric synthesis of an intermediate for the synthesis of Mannostatin A (as we reported in Trost and Van Vranken, "A Flexible Strategy to Polyfunctional Cyclopentanes. A Synthesis of Mannostatin A", *J. of Am. Chem. Soc.*, *113*, 6317-6318 (1991). Mannostatin A is a highly specific non-toxic inhibitor of α-D-mannosidase, and thus this glycosidase inhibitor has potential as an antiviral agent, as well as possibly an antimedistatic, anti-tumor proliferative, or an immunoregulatory agent. Mannosidase inhibitors, in particular, have been suggested as potential anti-HIV agents.

Example 10 illustrates the retrosynthetic analysis for the chemo-, regio-, and diastereoselec-

tivity of introduction of three different heteroatom functions on each and every carbon of a cyclopentane, and thus is a procedure that may be used to make carbanucleoside intermediates asymmetrically since the cyclopentane is a key intermediate towards pseudomonosaccharides. The best mode contemplated for carrying out this invention is building substituted five membered carbocyclic rings with varying substituted patterns with high enantioselectivity. Example 10 illustrates use of the invention to make a carbanucleoside in which use of inventive ligand 6.28 permitted the excellent enantiomeric excess of 96%. $[\alpha]_D^{25}$+111(c 4.57, $CHCl_3$ (1 mol% $(dba)_3 Pd_2 \cdot CHCl_3$, 3 mol% ligand, THF, quantitative yield) of the 1R,2S enantiomer, as determined by comparison of rotations to a sample whose ee was established by the O-methylmandelate ester nmr shifts determined on a transformation product derived therefrom.

Thus, use of the inventive ligand permits highly flexible strategies for the controlled introduction of heteroatoms around a cyclopentane nucleus.

EXAMPLE 10

(+)-3-Benzenesulfonyl-*cis*-3a-dihydro-4H-cyclopent[d]isoxazole-2-oxide.

To a mixture of $Pd_2(dba)_3(CHCl_3)$ (200.0 mg, 0.193 mmol) and chiral ligand 6.27 (320.0 mg, 0.464 mmol), THF (15 mL) was added. The mixture was stirred for 60 minutes and then cooled to 0°C. A solution of 1-cyclopentene-3,5-dibenzoate (5.96 g, 19.4 mmol) and lithium nitronate (4.41 g, 21.3 mmol) in 50 mL of THF (warming was necessary for the dissolution) cooled to 0°C was cannulated into the catalyst solution over a period of 10 minutes. After 3 hours, the reaction mixture was partitioned between ethyl acetate (300 mL) and aqueous sodium bisulfate (10%, 100 mL). The organic

layer was further washed with saturated sodium bicarbonate (100 mL) and saturated sodium chloride solutions, dried (magnesium sulfate) and evaporated *in vacuo* to give an oil. A solution of the product in 100 mL of 1:1 hexanes and ethyl acetate was filtered through a 10-cm silica gel column, washed with 2:1 hexanes/ethyl acetate to get rid of the black color. The filtrate was evaporated to give a yellow oil which solidified. After recystallization from 30% ether/hexanes, the tilted product was obtained as a white solid (4.84 g, 94.4%). $[\alpha]_D$=111.05° (C=4.57, $CHCl_3$), 96.0% ee for this batch.
IR (film): 1609, 1583, 1447, 1337, 1199, 1175.
^1H NMR (300 MHz, $CDCl_3$): δ 7.59-810(m, 5H), 6.24(m, 1H), 5.85(m,1H), 5.73(d, J=9.3Hz) 4.42(m,1H), 2.97(m, 2H).
^{13}C (75 MH, $CDCl_3$): 138.6, 138.1, 135.3, 129.8, 129.3, 127.9, 120.4, 86.3, 45.5, 38.7.
MS: 265 (M+/e,71), 219(54), 160(13), 141(46), 77(100).

(+)-3-Benzenesulfonyl-*cis*-3a,6a-dihydro-4H-cyclopent[d]isoxazole-2-oxide.

To the above *N*-oxide (4.75 g, 17.9 mmol) dissolved in 100 mL of acetonitrile was added 10.0 g (3 eg., 52.9 mmol) of stannous chloride. The suspension was stirred at r.t. for 6 hours. The reaction mixture was filtered through a Celite pad and the filtrate was evaporated. The residue was taken up in ethyl acetate and insoluble materials were again removed by filtration. The ethyl acetate filtrate was washed sequentially with saturated sodium bicarbonate and sodium chloride solutions, dried over magnesium sulfate, and filtered, and the solvent was removed *in vacuo*. The crude product was purified by flashing chromatography on silica gel, elution with 4:1 hexanes/ethyl acetate to give 4.15 g (93.0%) of the title compound. $[\alpha]_D$=183.08° (c=4.69, $CHCl_3$).

IR (film): 3068, 2929, 2866, 1583, 1561, 1447, 1329, 1311, 1159.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00(d, J=7.2Hz, 1H), 7.74(t, J=7.15Hz, 1H), 7.60(t, J=7.2Hz, 2H), 6.09(m, 1H), 5.91(dd, J=9.3, 1.1Hz, 1H), 5.82(m, 1H), 4.20(td, J=9.6, 1.9Hz, 1H), 3.10(dt, J=18.7, 2.0Hz, 1H), 2.83(ddt, J=18.7, 8.3, 2.3Hz, 1H).

^{13}C (75 MHz, $CDCl_3$): 162.0, 139.0, 135.9, 135.2, 129.9, 129.4, 128.5, 95.7, 48.6, 36.8.

MS: 249 (M+/e,11), 220(44), 143(27), 108(68), 77(100).

Anal. Calc'd for $C_{12}H_{11}NO_3S$: C,57.82; H,445; N,5.61; MW, 2249.0160. Found: C,57.88; H,4.26; N,5.51; MW, 249.01060.

(+)-3-Methoxy-*cis*-3a,6a-dihydro-4H-cyclopent[d]isoxazole-2-oxide.

A suspension consisting of the above benzensulfonylisoxazole (4.00g, 16.1 mmol) and excess well-pulverized potassium carbonate (12.0 g) in anhydrous methanol (80 mL) was heated at reflux for 3 hour. Methanol was removed by evaporation *in vacuo*. The organic material was taken up in ethyl acetate, washed with dilute sodium chloride solution twice and dried over magnesium sulfate. Filtration and concentration *in vacuo* gave a clear oil, which was purified by flash chromatography (4:1 hexanes/ethyl acetate as eluent) to afford the title compound (1.90 g, 85.1%). $[\alpha]_0$=122.05° (c=3.33, $CHCl_3$).

IR (film): 2923, 2852, 1625, 1448, 1368, 1351, 1002.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01(dd, J=5.7, 2.8Hz, 1H), 5.80(dd, J=5.7, 2.1Hz, 1H), 5.68(d, J=8.4Hz, 1H), 3.85(s, 3H), 3.73(ddd, J=8.4, 6.3, 2.9Hz, 1H), 2.64(m, 2H).

^{13}C (75 MHz, $CDCl_3$): 169.4, 133.9, 130.4, 91.4, 57.5, 46.6, 35.5

MS: 139(100), 124(37.8), 111(19.1), 110(19.9), 106(22.0), 97(66.0), 82(93.0).
HRMS: Calc'd for $C_7H_9NO_2$: 139.0633. Meas'd: 139.0628.

(-)-Methyl(1S,2R)-2-hydroxy-3-cyclopentene-1-carboxylate.

$Mo(CO)_6$ (251 mg, 0.951 mmol) was added to a solution of the above 3-methoxyisoxazoline (240 mg, 1.73 mmol) in acetonitrile/water (30:1, 31 mL) containing 320 mg (5.24 mmol) of boric acid under nitrogen. After heating at reflux for 7 h, silica gel (1.0 g) and methanol (10 mL) were added with stirring continued in the open air for an additional 3 h. The entire mixture was filtered through a plug of silica gel and the latter washed with ethyl acetate. Concentration of the filtrate *in vacuo* left a dark oil which was chromatographed on silica gel with a gradient elution (3:1 to 1:1 hexanes/ethyl acetate) to afford 205 mg (84%) of the titled hydroxy ester.
^1H NMR (300 MHz, $CDCl_3$): δ 6.06(dd, J=5.7, 3.0Hz, 1H), 5.87(dd, J=5.7, 4.8Hz, 1H), 4.97(bs, 1H, OH), 3.77(s, 3H), 3.23(dd, J=7.2Hz).
^{13}C (75 MHz, $CDCl_3$): 173.9, 135.2, 132.1, 77.1, 52.1, 47.9, 33.6.

(-)-(1R,2R)-1-Hydroxymethyl-3-cyclopentent-2-ol.

To a stirred suspension of lithium aluminum hydride (377 mg, 10.2 mmol) in anhydrous ether (30 mL) was added slowly a solution of the above hydroxyester (414 mg, 2.69 mmol) in 10 mL of ether. The mixture was stirred at rt for an additional hour. Water (377 μL) was added carefully followed by 15% NaOH (377 μL) and more water (1.13 mL). The mixture was stirred vigorously for 1 h, filtered through a plug of celite and washed with ethyl acetate. Filtrate was dried over $MgSO_4$, filtered and concentrated on rotary evaporator to

give a clear oil. This product was purified by flash chromatography on silica gel column eluted with 1:1 to 1:3 hexanes/ethyl acetate to afford 291 mg (95% yield) of the title diol [α]--130.19° (c:2.91, $CHCl_3$).

IR (film): 3385, 3073, 2924, 2856, 1655, 1615, 1410, 1336, 1307, 1112, 1045, 1010.

^1H NMR (200 MHz, $CDCl_3$): δ 5.95(m, 1H), 5.76(m,1H), 4.85(bd, J=7.0Hz, 1H), 3.73(dd, J=7.0, 5.3Hz, 2H), 3.25(bs, 1H), 2.37(dd, J=14.1, 8.0Hz, 1H), 2.27 (dtd, J=8.0, 2.2, 0.8Hz, 1H), 2.16 (dd, J=14.1, 2.2Hz, 1H).

^{13}C (50 MHz, $CDCl_3$): 135.5, 132.5, 77.5, 62.5, 42.4, 33.4.

MS: 114(1.4), 105(1.5), 96(99.9), 83(100), 81(23.4), 78(11.9), 73(3.9), 66(63).

HRMS: Calc'd for $C_6H_{10}O_2$: 114.0681; Meas'd: 114.0697.

(-)-(1R,2R)-1-Methoxycarboxymethyl-2-methoxycarboxy-3-cyclopentene.

To a stirred solution of the above diol (226 mg, 1.98 mmol) in THF (6.0 mL) at -78°C was added slowly n-BuLi (1.5 M, 3.30 mL, 4.95 mmol). The mixture was kept at -78°C, methyl chloroformate (461 μL, 5.94 mmol) was added via a syringe. After 20 minutes at -78°C, the dry-ice acetone bath was removed and the temperature allowed to rise to rt. The reaction mixture was poured into 50 mL of ether. The ethereal phase was washed with 10% $NaHSO_4$, saturated $NaHCO_3$ and NaCl solutions, and then dried over $MgSO_4$. Filtration and concentration left a yellow oil, which was purified by flash chromatography (6:1 to 4:1 hexanes/ethyl acetate) to give 445 mg (97% yield) of the bicarbonate [α]=-153.89° (c=3.75, $CHCl_3$).

IR (film): 2960, 1746, 1444, 1348, 1331, 1282, 1258, 1121, 948, 792.

^1H NMR (200 MHz, $CDCl_3$): δ 6.10(ddd, J=5.6, 2.3, 2.2Hz, 1H), 5.88(dd, J=5.6, 2.2Hz, 1H), 5.55(d, J=6.8Hz, 1H), 4.29(dd, J=10.7, 8.0Hz, 1H), 4.18(dd, J=10.7, 7.1Hz,

1H), 3.73(s, 3H), 3.70 (s, 3H), 2.69 (ddd, J=8.0, 7.1, 6.8Hz, 1H), 2.44 (m, 1H), 2.3 (m, 1H).
^{13}C (50 MHz, $CDCl_3$): 155.8, 155.5, 137.9, 129.0. 82.0, 66.7, 54.7, 54.6, 39.6, 34.3.
MS: 230(<0.1), 202(<0.1), 154(7.5), 110(21.0), 109(24.8), 95(37.2), 84(15.4), 80(14.1), 79(96), 78(100).

9-[(1'R,4'S)-4-(Methoxycarboxymethyl)-2-cyclopenten-1-yl]adenine.

To a solution of $Pd(OAc)_2$ (12.0 mg, 0.0536 mmol) in THF (0.5 mL) was added triisopropylphosphite (106 μL, 0.429 mmol), immediately followed by a n-BuLi (1.5 M, 107 μL, 0.161 mmol). After 15 minute, adenine (300 mg, 2.22 mmol, predissolved in 2 mL of dry DMSO) and the above bicarbonate (226 mg, 0.983 mmol, dissolved in 1 mL THF) was sequentially added. After stirring at rt for 4 hours, the solvents were removed. The dark residue was taken up in EtOH-CH_2Cl_2 (2:1), the insoluble materials were filtered off, and the filtrate was concentrated *in vacuo*. Purification by flash chromatography on silica gel eluted with 10% EtOH/CH_2Cl_2 afforded 260 mg (92% yield) of the titled compound. A white solid was obtained after recrystallization from CH_2Cl_2 and ether, m.p. 155-156°C, $[\alpha]_D^{25}$=-44.76° (c=4.72, $CHCl_3$).
IR (KBr): 3300, 3150, 1744, 1676, 1607, 1569, 1475, 1439, 1331, 1305, 1274, 957.
^1H NMR (300 MHz, $CDCl_3$): δ 8.31(s, 1H), 7.87(s, 1H), 6.4(bs, 2H), 6.11(ddd, J=5.7, 2.2, 2.0Hz, 1H), 5.91(ddd, J=5.7, 2.2, 2.1Hz, 1H), 4.24(dd, J=10.8, 5.3Hz, 1H), 4.13(dd, J=10.8, 5.2Hz, 1H), 3.73(s, 3H), 3.16(m, 1H), 2.88(ddd, J=14.1, 8.9, 8.9Hz, 1H), 1.68(ddd, J=14.1, 5.7, 5.6HMz, 1H).

^{13}C (75 MHz, $CDCl_3$): 156.4, 156.3, 153.6, 153.0. 150.4, 139.4, 137.7, 131.3, 120.3, 70.0, 59.4, 55.3, 44.9, 35.2.

Anal. Calc'd for C,53.97; H,5.23; N,24.21; Found: C,53.86, H,5.37; N,24.00.

9-[(1'R,4'S)-4-(Hydroxymethyl)-2-cyclopenten-1-yl]adenine.

The above carbonate (105 mg, 0.363 mmol) in 2 mL of ethanol was treated with 0.5 mL of 10% NaOH at rt for 2 hours. The mixture was neutralized with NH_4Cl to pH 8 and the solvents were removed *in vacuo*. The residue was taken up in absolute EtOH and the insoluble salt was removed by filtration. The filtrate was concentrated and then purified by chromatography on silica gel with a gradient elution using 10% to 30% EtOH/CH_2Cl_2. Recrystallization from absolute methanol gave 82.0 mg (98% yield) of the titled compound as a white solid, m.p. 194-196°C, $[\alpha]_D^{25}$=-4.57° (c=.75, EtOH).

IR (KBr): 3270, 3150, 3110, 1681, 2661, 1606, 1509, 1478, 1413, 1096.

^1H NMR (300 MHz, DMSO-d_6): δ 19(s, 1H), 8.13(s, 1H), 8.13(s, 1H), 6.21(dd, J=3.2, 2.3Hz, 1H), 5.94(dd, J=5.5, 2.3Hz, 1H), 5.68(dd, J=5.5, 4.1Hz, 1H), 3.61(m, 2H), 3.02(m, 1H), 2.88(ddd, J=9.0, 8.9, 6.9Hz, 1H), 1.74(ddd, J=13.8, 6.6, 4.9HMz, 1H).

^{13}C (75 MHz, DMSO-d_6): 157.7, 153.9, 150.6, 141.2, 140.4, 130.8, 120.5, 65.4, 61.4, 49.2, 35.5.

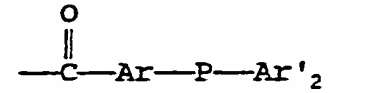
It is to be understood that while the invention has been described above in conjunction with preferred specific embodiments, the description and examples are intended to illustrate and not limit the

scope of the invention, which is defined by the scope of the appended claims.

It is Claimed:

1. A ligand, useful for transition metal catalyzed bond forming reactions, comprising:

a metal binding portion bound to a chiral scaffold, the chiral scaffold derived from an asymmetric alcohol or an asymmetric amine, the metal binding portion having at least one metal binding moiety with the structure



wherein Ar and Ar' each is an aryl or a heteroaryl with a single ring or fused rings.

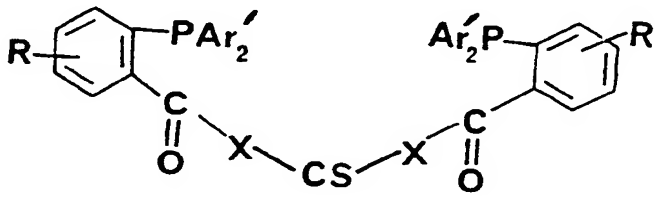
2. The ligand as in claim 1 wherein the metal binding portion and the chiral scaffold are covalently bound with two or three metal binding moieties for each chiral scaffold.

3. The ligand as in claim 1 wherein the chiral scaffold and the metal binding portion are bound through an ester linkage when the chiral scaffold is derived from an alcohol and through an amide linkage when the chiral scaffold is derived from an amine.

4. The ligand as in claim 1 wherein each of Ar' is a five or six membered ring containing one or none of nitrogen, oxygen, or sulfur atoms in addition to carbon.

5. The ligand as in claim 1 wherein the chiral scaffold is a tartrimide.

6. The ligand as in claim 1 wherein the chiral scaffold is derived from a bis-alcohol or a bis-amine and the ligand has the structure



wherein CS is the chiral scaffold, X is O or is NH, and R is H or is an alkyl, a halide or an alkoxy substituent.

7. A ligand, capable of forming C_2 symmetrical complexes with a transition metal for catalysis of bond forming reactions, comprising:

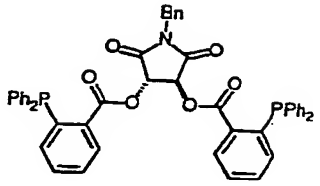
an aryl or a heteroaryl carboxylic acid derivative, the derivative having a diarylphosphino substituent or a diheteroarylphosphino group on the aryl or heteroaryl moiety.

8. The ligand as in claim 7 wherein the aryl or the heteroaryl carboxylic acid derivative is an ester or an amide derived from a chiral diol or a chiral diamine.

9. The ligand as in claim 7 wherein the phosphino substituent is ortho with respect to the carbonyl group of the carboxylic acid derivative.

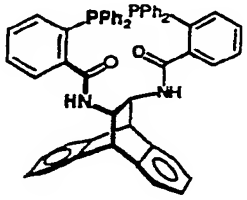
10. The ligand as in claim 7 wherein the aryl or heteroaryl moiety includes a plurality of fused rings.

11. The ligand as in claim 1 or 7 having the structure



wherein Ph is phenyl and Bn is benzyl, aryl, or alkyl.

12. The ligand as in claim 1 or 7 having the structure



13. A method for preparing ligands, useful for transition metal catalyzed bond forming reactions, comprising:

providing an aromatic carboxylic acid having a diarylphosphino or a diheteroarylphosphino substituent on the aromatic ring; and

forming an ester or an amide derivative of the carboxylic acid by coupling with a chiral diol or a chiral diamine in the presence of dicyclohexyl-carbodiimide.

14. The method as in claim 13 wherein the phosphino substituent is ortho with respect to the carbonyl group of the carboxylic acid.

15. The method as in claim 13 wherein the aromatic carboxylic acid has a plurality of fused rings.

16. The method as in claim 13 wherein the ring of the aromatic carboxylic acid includes a heteroatom.

17. The method as in claim 13 wherein the chiral diol is N-substituted tartriimide.

18. A method for synthesizing cyclopentane analogues of carbohydrates, comprising:

asymmetrically introducing heteroatoms around a cyclopentane nucleus of an intermediate while controlling the introduction by inducing an enantiomeric excess, the controlling including contacting the intermediate with a transition metal and a ligand for the transition metal, the ligand having a metal binding portion bound to a chiral scaffold, the chiral scaffold derived from an asymmetric alcohol or an asymmetric amine, the metal binding portion being an aryl carboxylic acid derivative or a heteroaryl carboxylic acid derivative, the derivative having an aromatic phosphino substituent on the aryl or on the heteroaryl moiety.

19. The method as in claim 18 wherein the cyclopentane analogue synthesized is a glycosidase inhibitor.

20. The method as in claim 18 wherein the aryl or the heteroaryl acid derivative binds the transition metal with C_2 symmetry.

21. The method as in claim 18 wherein the chirality of the ligand is selected to correspond to the absolute stereochemistry desired in the transition metal catalyzed reaction.

CORRECTED VERSION*

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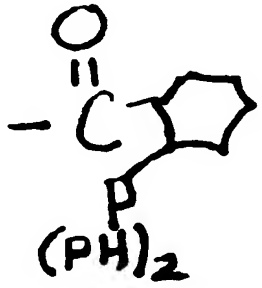

(I)

(57) Abstract

Chiral ligands useful for transition metal catalyzed bond forming reactions are provided with a metal binding portion having two metal binding moieties each with the structure (I). These two groups are spaced within the ligand connecting these two groups which variously are aliphatic, aromatic or saccharide groups which are chiral diols and chiral diamines so that diester or diamido derivatives of the above metal binding moiety are formed. These chiral ligands are used to form five-membered carbocyclic rings variously substituted with high enantioselectivity.

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